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Review of Terms for Regulated versus Forced Neurochemical-Induced Changes in Body Temperature

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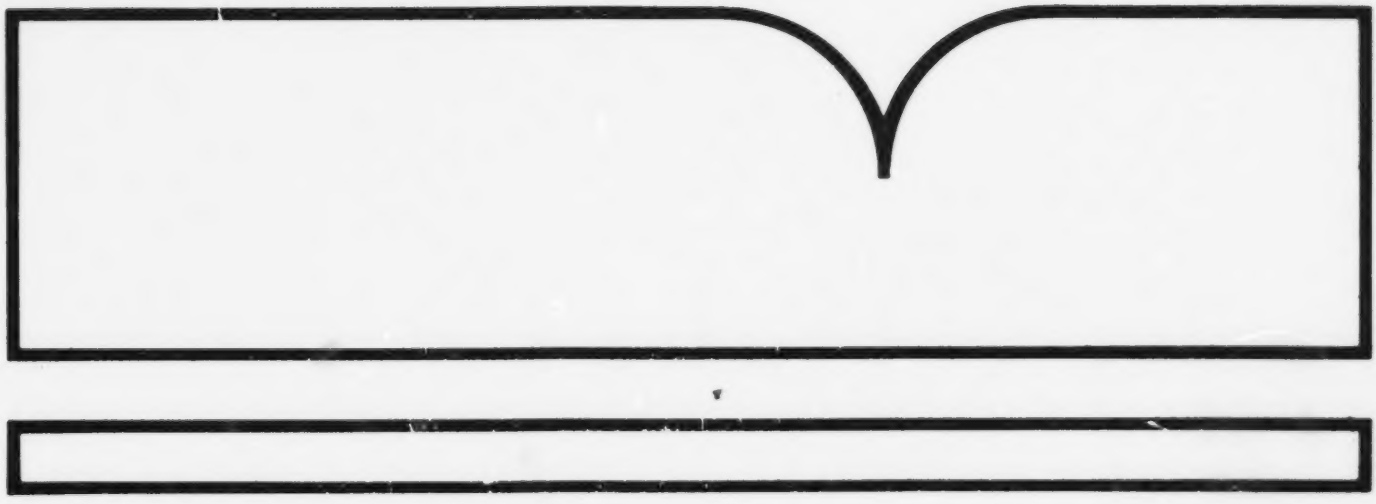

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16. ABSTRACT

Deviations of the body temperature of homeothermic animals may be regulated or forced. A regulated change in core temperature is caused by a natural or synthetic compound that displaces the set-point temperature. A forced shift occurs when an excessive environmental or endogenous heat load, or heat sink, exceeds the body's capacity to thermoregulate but does not affect set-point. A fever is the paradigm of a regulated increase in body temperature, but the term fever has acquired a strict pathological definition over the past two decades. Consequently, other forms of nonpathological regulated elevations in body temperature have generally been classified as hyperthermia; and decreases in core temperature--either forced or regulated vs. a forced temperature change, a confusion of terms has been created in the literature. It would appear that "resisted or unregulated hyperthermia" and "hypothermia," respectively, are appropriate terms for describing a forced increased and decrease in core temperature. A nonpathological but regulated elevation in temperature may be defined as unresisted or regulated hyperthermia, whereas a regulated decrease in temperature may be termed unresisted or regulated hypothermia. This simple scheme appears to be the most practical means for distinguishing between forced and regulated changes in core temperature.

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MINIREVIEW

A REVIEW OF TERMS FOR REGULATED VS. FORCED, NEUROCHEMICAL-INDUCED CHANGES IN BODY TEMPERATURE

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Summary

Deviations of the body temperature of homeothermic animals may be regulated or forced. A regulated change in core temperature is caused by a natural or synthetic compound that displaces the set-point temperature. A forced shift occurs when an excessive environmental or endogenous heat load, or heat sink, exceeds the body's capacity to thermoregulate but does not affect set-point. A fever is the paradigm of a regulated increase in body temperature, but the term fever has acquired a strict pathological definition over the past two decades. Consequently, other forms of nonpathological, regulated elevations in body temperature have generally been classified as hyperthermia; and decreases in core temperature--either forced or regulated--have generally been classified as hypothermia. Since the terms hyperthermia and hypothermia fail to distinguish a regulated vs. a forced temperature change, a confusion of terms has been created in the literature. It would appear that "resisted or unregulated hyperthermia" and "hypothermia," respectively, are appropriate terms for describing a forced increase and decrease in core temperature. A nonpathological but regulated elevation in temperature may be defined as unresisted or regulated hyperthermia, whereas a regulated decrease in temperature may be termed unresisted or regulated hypothermia. This simple scheme appears to be the most practical means for distinguishing between forced and regulated changes in core temperature.

The usually stable, deep-body temperature of homeothermic animals can be affected by innumerable biological and physical agents. Neurotransmitters, neuromodulators, synthetic drugs, and electrolytes, to name a few, will cause an elevation or depression in body temperature depending on the dose, species, and route of administration (1,2,3,4). Physical factors such as environmental temperature, altitude, and photoperiod play a complex role in governing the level of deep-body temperature (5).

Body temperature can change if one or a combination of two principal mechanisms are operative: (i) an alteration in the apparent "set-point" temperature, resulting in a regulated shift, or (ii) an excessive environmental or endogenous heat load, or heat sink, overwhelming the animal's capacity to thermoregulate, and resulting in a forced shift in temperature. In the former case, the change in temperature is generated with a coordinated set of physiological responses whereby the preferred operating core temperature has shifted in a regulated or controlled fashion. In the latter case, body temperature is changing against the animal's preferred level. That is, the

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motor outputs are working against but are overwhelmed by thermal stress; therefore, the shift in body temperature is classified as forced.

Fever is the paradigm of a regulated change in body temperature. Administration of bacterial and other infectious pyrogens will result in peripheral vasoconstriction and shivering followed by a concomitant elevation in deep-body temperature (6,7,8). Also, numerous nonpathological substances elicit regulated fever-like shifts in body temperature. In addition, some compounds injected into the central nervous system (CNS) or systemically will evoke non-regulated or forced changes in body temperature (infra vide).

The nomenclature of neuropharmacology has not kept pace with the study of temperature-active compounds. Other than "fever" the only term adequate for describing an elevation in body temperature is "hyperthermia." On the other hand, "hypothermia" is the only available term for describing a depression in body temperature. "Hypo-" and "hyperthermia" do not convey the distinction between a regulated and a forced change in body temperature. For instance, an intramuscular injection of norepinephrine (NE) in the rat stimulates metabolism resulting in a large endogenous heat load and a subsequent increase in body temperature (9); whereas a hypothalamic injection of NE in the rabbit promotes peripheral vasoconstriction followed by a fever-like rise in body temperature (10). The former example represents a forced and the latter a regulated increase in core temperature; should both responses be classified as hyperthermic?

Lack of proper nomenclature for describing pharmacological and other forms of regulated and forced increases in body temperature has created confusion. In addition, the lack of conventional nomenclature for distinguishing between regulated and nonregulated decreases in body temperature has also created inconsistencies in the literature. A glossary of terms for thermal physiology (11) is currently under revision (A.P. Gagge, personal communication). Therefore, it is pertinent that the nomenclature for identifying changes in body temperature be readdressed.

Mechanisms that Affect Thermal Homeostasis

A fundamental control scheme is useful for explaining the effects of temperature-active agents on thermoregulation. The complexities of the mammalian temperature regulatory system have been summed (12) into four principal components (Fig. 1): (i) a receptor component consisting of warm- and cold-sensitive neurons in the skin, deep body, and the CNS, (ii) the neural controllers responsible for comparing actual skin and deep-body temperatures with respective operating or "set-point" temperatures and eliciting the proper motor signals, (iii) the motor effectors including shivering, peripheral vasomotor control, behavioral regulation, and evaporative heat loss, and (iv) the passive component which refers to the temperature of all body components. It is important to note that use of the term "set-point" in temperature regulation is controversial. The presence or absence of a central neural mechanism to generate a "set-point" or "reference" temperature has stimulated an array of discussions (12,13,14,15). In the present paper, the author's use of "set-point" is a matter of convenience and it is not a condonation of its use in the literature. In this paper, "set-point" refers to the regulated or preferred level of body temperature.

A scheme similar to that in Fig. 1 was used (1) to explain how a drug or natural neurotropic substance could affect body temperature. A compound can directly affect the neural controller and subsequently alter the set-point. For instance, elevating the set-point above normal creates a situation where the animal reacts as if it were cold. Depending on ambient temperature, the

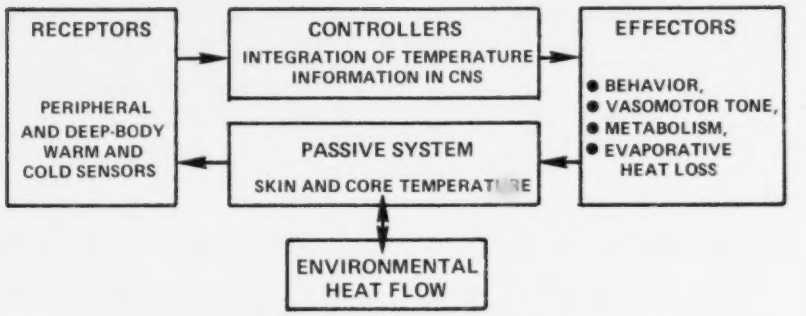

FIG. 1

Summary of the major components of thermoregulatory control. Temperature-active compounds can affect temperature of the passive system by modulating activity of the receptor, controller, and/or effector components (modified from Werner [12]).

animal will vasoconstrict, shiver, and/or reduce evaporative heat loss concomitantly with an elevation in body temperature. When temperature reaches the new level, as influenced by the new set-point, the animal exhibits normal thermoregulatory responses but at a higher body temperature. Reducing the set-point creates a situation where the organism acts as if it were heat stressed. This is characterized by peripheral vasodilation, increased evaporative heat loss, and/or behavioral selection of a cooler environment and, hence, a reduction in body temperature. The heat-dissipating effectors lower temperature toward the displaced set-point, at which time normal thermoregulatory reflexes operate at a lower body temperature.

A drug or natural neurotropic compound can cause a regulated change in body temperature by modulating the activity of the thermal-afferent pathways. For example, in the absence of thermal stimulation, exciting the cold thermosensor pathway will drive heat-conserving mechanisms, suppress heat-dissipating mechanisms, and subsequently elevate body temperature. As temperature rises the components of the warm-sensor pathway become excited and nullify the activated cold-sensor pathway. Removal of the cold pathway stimulus allows unimpeded activation of the warm-afferent pathway resulting in heat dissipation and a return of body temperature to euthermia. This response is similar to an elevation in set-point, since the regulated temperature is pushed to a higher level through endogenous stimulation of the cold-sensitive pathway. A similar pattern is observed when the anterior brain stem, midbrain, medulla, or spinal cord is locally cooled with a stereotaxically implanted thermode (16,17). A response similar to a reduction in set-point will occur if the warm-afferent pathway is chemically stimulated or if warm-sensitive neurons in the CNS are locally warmed.

The final mode of action involves agents that selectively excite or inhibit the effector systems. For example, a systemic injection of NE in mammals causes a large increase in metabolism and a subsequent increase in deep-body and skin temperatures. Because the thermal sensors and controller neurons are unaffected by the systemic injection, heat-dissipating effectors are activated in an attempt to return body temperature to euthermia. Contrarily, a curarized animal is presumably capable of sensing temperature stimuli and delivering nerve impulses to the proper effector organs but still loses body heat because of the paralyzed condition of the cholinergic synapses. Recently, the term "poikilothermia" was used (18) to identify a condition where a CNS depressant

(ethanol in this case) induced both passive hypothermia and passive hyperthermia. Poikilothermia in a homeotherm could be induced with a simultaneous depression of activity of neurons involved in thermal sensation, integration, and/or effector activity. In summary, changes in body temperature induced by modification of effector mechanisms do not affect the ability to sense temperature. These types of temperature changes are largely dependent on ambient temperature. For example, inhibiting heat loss in the cold will have little effect, whereas similar inhibition in a hot environment will manifest an elevated body temperature.

Nomenclature for Conditions of an Elevated or Depressed Temperature

In 1875, the thermoregulatory role of fever was recognized and defined (19) as: "... the name of a complex of symptoms based on the fact that the heat regulation is adjusted to a higher level." Recent discussion of the term "fever" is available (20,21).

Preceding the 1960's, it was thought that a regulated increase in body temperature could be produced only through an infectious-type fever. However, in 1963 a ventricular injection of 5-hydroxytryptamine (5-HT) in the cat was reported (22) to promote shivering and a "fever." In a later study (10), a ventricular or direct hypothalamic injection of NE or epinephrine was shown to result in peripheral vasoconstriction followed by a prolonged rise in body temperature; these investigators referred to the monoamine-induced rise in temperature as a fever.

Monoamine shifts in core temperature can differ from infectious fevers in that the temperature effects of the amine are dependent on ambient temperature. Infectious fevers typically cause a uniform elevation in core temperature at most ambient temperatures (23). On the other hand, a CNS injection of NE in the rabbit results in an elevated core temperature at a high ambient temperature and a depressed temperature in the cold (24). Hence, the responses to monoamines and other nonpathological agents that raise body temperature have a passive effect in that they depend on ambient temperature. However, because of the coordinated physiological response (i.e., vasoconstriction and reduction in evaporative heat loss), the elevation in temperature is apparently a regulated phenomenon.

Since the early work with the monoamine neurotransmitters, a multitude of compounds, including natural CNS substances and drugs, has been reported capable of eliciting a fever-like increase in body temperature (1,2,3). Despite these studies, the most recent glossary of terms for thermal physiology incorporated a pathological cause into the definition of fever (11): "A pathological condition in which there is an abnormal rise in core temperature ... the temperature rise in an individual may be considered as fever when it is greater than the mean standard deviation for the species in basal conditions."

According to this pathological definition of "fever," no other term exists for physiologists and pharmacologists to describe the actions of a nonpathological substance that promotes a regulated increase in body temperature. In reviews on the effects of opioid peptides on temperature regulation, the term "hyperthermia" was used (25,26) to describe any response involving an elevation in deep-body temperature. Other recent reviews on the pharmacology of temperature regulation describe the response as hyperthermia and/or increase in body temperature (1,2,3,4). Use of the terms "increase in temperature" and "hyperthermia" does not distinguish a compound that affects the set-point from one that directly increases thermogenesis and/or increases heat retention (i.e., a forced elevation in body temperature).

It has been asserted (23) that fever and hyperthermia (resulting from, e.g., exercise, heat stress, or pharmacological agents) could be distinguished by several criteria: (i) The elevation in temperature during fever is regulated and defended by thermoregulatory mechanisms, (ii) the thermopreferendum is elevated with fever, and (iii) aspirin-like drugs can inhibit a temperature rise during fever but not with other cases of elevated temperature. However, other data suggest that these three criteria do not necessarily distinguish fever from hyperthermia. Firstly, a regulated elevation in temperature is not unique to fever and will occur following the injection of numerous nonpathological substances (supra vide). Secondly, an elevation in the thermopreferendum occurs when numerous nonpathological compounds are injected into the CNS (27). For example, a preoptic injection of NE raises body temperature in the rat; however, the elevation in temperature is accompanied by an increase in lever pressing for heat (28). If NE were simply elevating motor activity and not affecting set-point, one would expect heat-seeking behavior to decrease rather than increase. Thirdly, some nonpyrogenic compounds which raise body temperature can be antagonized with aspirin-like drugs. For example, the thermal effects of thyrotropin-releasing hormone (29) and 5-HT (30) can be blocked with indomethacin. In one case, aspirin-like compounds have been found to be ineffective against a leucocytic pyrogen-induced fever (31).

An attempt was made (1) to classify the effects of neurotropic agents on body temperature into active and passive modes. For example, inhibition of heat generation in the cold could be classified as passive hypothermia and, similarly, inhibition of heat dissipation at a high ambient temperature could be defined as passive hyperthermia. An agent that raises body temperature in the cold would be causing an active hyperthermic response. Active hypothermia would be indicated when a compound reduced body temperature in a hot environment. However, an active and passive classification still does not satisfactorily distinguish between a regulated (i.e., modification of the controller or afferent component in Fig. 1) vs. a forced (i.e., modification of effector activity in Fig. 1) change in deep-body temperature.

Identifying a nonpathological but regulated elevation in body temperature as "hyperthermia" is indiscriminative, because this term does not differentiate a regulated from a forced increase in temperature. In a glossary for thermal physiology (11), hyperthermia was defined as: "The condition of a temperature-regulating animal when the core temperature is more than one standard deviation above the mean core temperature of the species in resting conditions in a thermoneutral environment (Gk. hyper:over; therme:heat)." The same authors also noted that a nonpathological hyperthermia occurred when "... the regulatory centers might be functioning normally but the heat load may be too great to be compensated by equal heat loss without a rise in core temperature ..." Hence, a fever can be classified as hyperthermia, but not all cases of hyperthermia are necessarily fevers. For example, if body temperature increases because of an uncontrolled increase in metabolism or from exposure to ambient heat stress, the individual is considered hyperthermic but not febrile. Considering that a nonpathological compound such as 5-HT promotes a fever-like regulated increase in body temperature, should this response be classified as hyperthermia? Although the 5-HT response was originally defined (22) as a fever, the current pathological definition of fever precludes placing the 5-HT response under the same category.

What of the classification of agents that promote regulated decreases in body temperature? Can hypothermia be used to identify the effect of any drug that lowers body temperature? For instance, a CNS injection of 5-HT in the rabbit (10) and NE in the cat (7,22) results in a reduced set-point that is characterized by vasodilation and a reduction in body temperature. On the other hand, injecting the polypeptide bombesin into the rat CNS causes a rapid inhibition

of metabolism and drop in body temperature (32). Referring to the glossary of thermal terms (11), hypothermia is defined as: "The condition of a temperature-regulating animal when the core temperature is more than one standard deviation below the mean core temperature of the species in resting conditions in a thermoneutral environment (Gk. hypo:under; therme:heat)." Injecting the monoamine neurotransmitters into the CNS affects the thermal controller and causes a reduction in the set-point, whereas the bombesin affects only the organism's ability to generate heat. In both cases the reduction in body temperature fits with the above definition of hypothermia; however, it is clear that hypothermia per se does not satisfactorily distinguish between the monoamine-regulated and the bombesin-forced depressions in core temperature.

General Classification of Temperature Responses

Considering the immense number of drugs, natural neurotropic compounds, and physical agents that affect thermoregulation, along with anticipated future discoveries, a nomenclature must be developed that distinguishes between regulated and nonregulated changes in body temperature. There are six principal profiles of change in body and skin temperature that can be mediated by a biological or physical agent (Fig. 2). To elevate body temperature, heat gain must exceed heat loss; this may occur by one of three means: (A) exposure to intense ambient heat stress which drives skin temperature upward and subsequently increases core temperature, or (B) an endogenous elevation in heat production not affecting set-point which results in a simultaneous elevation of skin and core temperatures, or (C) a regulated increase in temperature where the set-point is elevated because either neural activity in the controller is affected or because the cold-afferent pathway is stimulated selectively and endogenously. The three principal ways to lower body temperature are (Fig. 2): (D) exposure to cold causing a reduction in skin and core temperature, (E) a forced decrease resulting from an inhibition of metabolism or increase in conductance and not affecting set-point, and (F) a regulated decrease that occurs when the set-point is directly lowered at the controller level or through endogenous stimulation of the warm-afferent pathway. Profiles A and D reflect typical temperature changes occurring when the organism is subjected to an excessive environmental heat load/sink. Profiles B and E exemplify temperature changes when a pharmacological compound influences only the effector mechanisms (e.g., Fig. 1). The response depicted in Profile B would occur if metabolic heat production increased, especially at a high ambient temperature. The response of Profile E could result after inhibiting metabolism, especially in the cold.

Examples A and B can certainly be classified as hyperthermia and responses D and E as hypothermia (Fig. 2). This is an appropriate classification, since in both cases there is an imbalance between heat gain and heat loss, while the receptors and integrative controllers operate normally. Changes in body temperature resulting from over- or underactive effectors clearly differ from the regulated temperature shifts, responses delineated by Profiles C and F in Fig. 2. Since "hypothermia" and "hyperthermia" are reserved to refer to the forced changes in body temperature, then how should responses of "set-point-effective" agents, including both pathological and nonpathological, be classified?

It is important to note that the temperature responses in Fig. 2 are not meant to be an all inclusive presentation. There are, of course, many variations that cannot all be illustrated. Occasions will arise when it will be extremely difficult to classify a temperature response as forced or regulated. The decision will have to be based on the presence of a coordinated series of physiological events which are listed in Table I. Depending on ambient

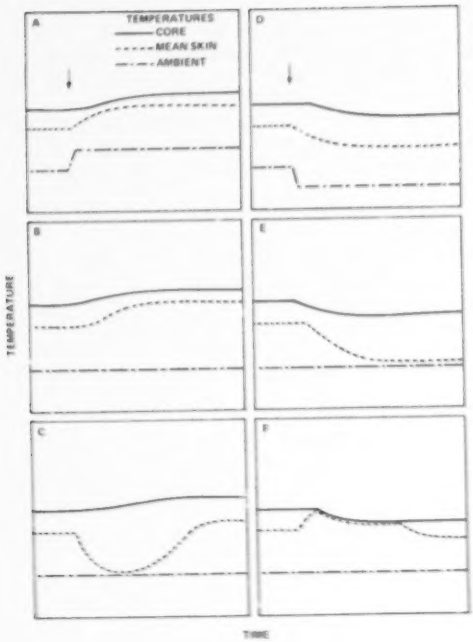

FIG. 2

Principal time-courses of core and skin temperature that are induced (at arrows) by physical or biological agents: (A) Forced increase in skin and subsequently core temperature caused by elevating ambient temperature; (B) forced increase in core and subsequently skin temperature caused by an uncontrolled increase in metabolism; (C) elevation in set-point, indicated by a reduction in peripheral heat loss followed by an increase in core temperature; (D) forced decrease in skin and subsequently core temperature resulting from exposure to cold stress; (E) forced decrease in core and subsequently skin temperature from an inhibition of metabolism; and (F) regulated decrease in core temperature, characterized by an increase in peripheral heat loss followed by a reduction in core temperature toward a lower set-point.

TABLE I

Required Activity Changes of Thermoregulatory Motor Outputs for Promoting Regulated Elevations or Depressions in Body Temperature

Parameter*	Temperature Elevation	Temperature Depression
Metabolic Rate	Increase†	Decrease
Evaporative Heat Loss	Decrease‡	Increase‡
Peripheral Vasomototor Tone	Increase‡	Decrease
Thermal Preferendum	Increase†‡	Decrease†‡
Piloerection	Increase	Decrease

*Most or all parameters must be measured to assure that the temperature shift is regulated and not forced.
†Of greater importance in a cold environment.
‡Of greater importance in a warm environment.

temperature, it will probably be necessary to measure most or all of these parameters during the time-course of change in body temperature in order to distinguish a forced from regulated response.

Suggested Terminology

"Fever" could be used to identify the effect of all substances that promote regulated elevations in body temperature. This is warranted by the 1875 definition (19), which had no pathological implication but simply referred to an elevation in the regulated temperature. Indeed, "fever" was originally used to identify the monoamine-induced elevations in body temperature (10,22). However, because "fever" is now commonly used for describing pathological elevations in body temperature, it seems inappropriate to set the nomenclature back 20 years and to use this term for nonpathological substances that cause upward displacements in set-point.

To the best of my knowledge there is no common term for identifying the response of an agent that causes a negative displacement in set-point. A substance in the urine of humans was recently reported to promote a decrease in the regulated temperature of rabbits when injected intravenously (33,34). The urinary material was described as a cryogen, since it induced a response exactly opposite to that of a fever. Hence, the time course of the depression in body temperature after administration of the urine extract would be termed "cryogenesis."

If the term "cryogen" is used to identify a nonpathogenic substance that lowers the set-point, other compounds can be termed cryogens, e.g., drugs and other natural neurotropic compounds that lower set-point. The next logical step would be to use the term "pyrogen" to identify any compounds which elevate set-point. The only problem with this type of nomenclature is that the current definition of pyrogen is closely related to febrogenesis and, therefore, connotes a pathological meaning (11): "The generic term for any substance whether exogenous or endogenous which causes a FEVER when introduced into or released in the body." However, the etymology of the word has no pathological implication (Gk. pur:fire; gen:to become). "Pyrogen," like "fever," has acquired pathological definitions, probably as a result of intense research on the mechanism of infection-induced rises in body temperature.

Recently, alternate terms for describing forced and regulated temperature responses have been proposed (Table II). Bligh (personal communication) suggested the terms "resisted hyper- and hypothermia" and "unresisted hyper- and hypothermia" be used to describe forced and regulated changes in temperature, respectively. Hensel (35) also recognized the lack of terminology for describing regulated decreases in temperature and subsequently used the term "central hypothermia," that is, a reduction in body temperature resulting from changes in activity of CNS temperature-integrating neurons. However, central hypothermia could be induced through CNS activation of effector systems without affecting set-point (Fig. 1). Thus, the terms "central hyperthermia or "central hypothermia" do not necessarily distinguish between forced and regulated response. Cabanac (36) proposed the term "anapyrexia" (reversed fever) to identify regulated decreases in temperature.

To summarize briefly, there is an array of factors--chemical compounds, physiological states, and environmental conditions--that promote shifts in body temperature and that distinctly fall under a classification of regulated change, as compared to temperature shifts brought on by an excessive environmental heat load/sink. Most would agree that the term "fever," because of its specific reference to infectious substances, should not be used to classify other types of regulated increases in temperature. Furthermore, there is not a unanimous consensus for a term describing regulated decreases in body temperature. From this author's point of view, it would be useful to have a set of terms with similar etymology that identifies regulated and forced increases and decreases in body temperature. Of all the suggested terms listed in Table II,

TABLE II

Summary of Proposed Nomenclature for Distinguishing Between Forced and Regulated Changes in Body Temperature

Temperature Increase	Temperature Decrease
Regulated	
Pyrogenesis (Pyrexia)	Cryogenesis*
Unresisted Hyperthermia†	Unresisted Hypothermia†
Central Hyperthermia	Central Hypothermia‡
Fever	Anapyrexia§
Regulated Hyperthermia	Regulated Hypothermia
Forced	
Hyperthermia	Hypothermia
Resisted Hyperthermia†	Resisted Hypothermia†
Unregulated Hyperthermia	Unregulated Hypothermia
Poikilothermia#	Poikilothermia#

*Kluger et al. (33,34). †Bligh (personal communication). ‡Hensel (35). §Cabanac (36). #Myers (18).

it would appear that the terminology should be derived from "hyperthermia" and "hypothermia." Regulated changes in body temperature may be described with the terms "unresisted" or "regulated hyperthermia and hypothermia." Forced changes in body temperature may be described with the terms "resisted" or "unregulated hyperthermia" and "hypothermia."

Resisted vs. unregulated and unresisted vs. regulated body temperature responses (Table II) are not necessarily identical. For example, body temperature can increase in an unresisted fashion (i.e., after exposure to high ambient temperature without increased activation of heat-dissipating effectors), but the response would not necessarily be classified as regulated. On the other hand, a regulated hyperthermia is unresisted in that the animal is not activating heat-dissipating effectors. However, during regulated hyperthermia, there is a coordinated activation of heat-generating/conserving effectors and inhibition of dissipating effectors. Hence, there are fine distinctions, in some cases, in the types of regulated changes in body temperature; some may be construed to be more of a passive rather than regulated process. The definitions in Table III are proposed to aid in the classification of various thermoregulatory responses.

It is this author's opinion that the proposed standard terms in Table III clearly distinguish regulated vs. forced changes in body temperature. This separation is very important to the field of environmental physiology, neurophysiology, and pharmacology. In a recent symposium on the role of neurotropic agents in thermoregulation, no less than 28 compounds including amines, peptides, and amino acids were listed with putative roles in the neurochemical control of body temperature (37). As current and future biological and physical temperature-altering agents are studied, a standard classification that segregates regulated and forced changes in body temperature will be essential.

TABLE III

Proposed Definitions of Selected Thermoregulatory Responses

Response	Definition
Unresisted Hyperthermia	- A significant elevation in body temperature (T_b) where there is no increased activation of heat-dissipating effectors
Unresisted Hypothermia	- A significant decrease in T_b where there is no increased activation of heat-generating/conserving effectors.
Resisted Hyperthermia	- A significant increase in T_b in spite of an increased activation of heat-dissipating effectors.
Resisted Hypothermia	- A significant decrease in T_b in spite of an increased activation of heat-generating/conserving effectors.
Regulated Hyperthermia	- A significant increase in T_b where there is an increased activation of heat-generating/conserving effectors and inhibition of heat-dissipating effectors.
Regulated Hypothermia	- A significant decrease in T_b where there is decrease in activity of heat-generating/conserving effectors and increase in heat-dissipating effectors.
Unregulated Hyperthermia	- Same as Resisted Hyperthermia.
Unregulated Hypothermia	- Same as Resisted Hypothermia.

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